Exhibit A

(Part 1 of 2)

UNITED STATES DISTRICT COURT

DISTRICT OF MASSACHUSETTS

Amgen Manufacturing, Limited; Immunex Rhode Island Corporation; and Amgen USA Inc., Plaintiffs, vs. The Trustees of Columbia University in the City of New York, a New York corporation, Defendant.	No. 04-12626-MLW **COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF RE: CONTRACT RIGHTS, INVALIDITY, UNENFORCEABILITY AND NON-INFRINGEMENT OF U.S. PATENT NO. 6,455,275 AND PREDECESSOR PATENTS**

For their Complaint, Plaintiffs Amgen Manufacturing, Limited ("Amgen Mfg."), Amgen USA Inc. ("Amgen USA") and Immunex Rhode Island Corporation ("Immunex R.I.") aver as follows:

INTRODUCTION

1. Amgen Mfg., Amgen USA, and Immunex R.I. (collectively "Plaintiffs"), who are affiliates of Amgen Inc. ("Amgen"), bring this action for a declaration that, contrary to the contentions of defendant, The Trustees of Columbia University in the City of New York ("Columbia"), Plaintiffs have no liability to Columbia for infringement of U.S. Patent 6,455,275 ("the '275 patent"), issued September 24, 2002, which is invalid, unenforceable and not infringed by Plaintiffs' activities.

2. Columbia secured four patents, the '216, '665, '017 and '275 patents (collectively, "the Axel Patents") from the U.S. Patent and Trademark Office ("PTO"), all based on the same patent application filed February 25, 1980. The first issued in 1983, and the next

two, which issued in 1987 and 1993, were terminally disclaimed by Columbia so that all three patents (collectively, "the prior issued Axel patents") expired on August 16, 2000. For license rights under the Axel patents during their life, pursuant to the license agreements with Columbia, Amgen and Immunex Corporation ("Immunex") paid more than 100 million dollars.

3. Columbia also secured corresponding foreign patents from patent offices in Europe, Canada and Japan, including European Patent No. 045,809, the national patents based on the European patent, and Japanese Patent No. 5700410. These patents expired on February 25, 2000, twenty years from their priority filing date. Columbia also obtained corresponding Canadian Patent No. 1179953, which expired on December 27, 2001.

4. After the prior issued Axel patents expired on August 16, 2000, Columbia demanded that Amgen and Immunex continue to pay royalties because Columbia had additional pending patent applications claiming priority to that 1980 patent application, one of which later matured into the '275 patent.

5. Twenty-two years after the filing of the original patent application, and two years after the prior issued Axel patents expired, a fourth patent – the '275 patent – was issued in September 2002, claiming priority from the same 1980 patent application, with claims that covered the same subject matter as the prior issued Axel patents. The term of the '275 patent extends to September, 2019, thereby potentially doubling the life of the patents issued from the same original patent application. Following issuance of the '275 patent, Columbia asserted that Amgen and Immunex continue to owe royalties under the licenses, based on the '275 patent. Columbia's position would require payment of royalties to Columbia essentially for the same claims for a total of 30 years. This constitutes a grossly improper extension of patent rights.

6. A necessary part of Columbia's allegation that Amgen and Immunex owe royalties by reason of the '275 patent is Columbia's assertion that their activities include the sale of products whose manufacture, use or sale is covered by a claim of the '275 patent. In fact, as described below, the pertinent activities of Amgen and Immunex are in part carried out by Plaintiffs, and thus Columbia's assertions also accuse the conduct of Plaintiffs. The license agreement between Columbia and Immunex expired on January 4, 2003, and thereafter the license agreement between Columbia and Amgen covered Immunex as well as Amgen's other affiliates. However, on March 9, 2004, Columbia purported to terminate its license agreement with Amgen, and if such termination were valid and proper (which it is not), Columbia's assertions as to the '275 patent amount to the assertion that Plaintiffs are infringing the '275 patent.

7. Additionally, Columbia has wrongfully purported to terminate the license agreement between Amgen and Columbia, based on claims to royalties that are unlawful and in fact are not owed. Columbia's own misconduct leading to the patents that were the subject of that license, as well as its other repressive practices as discussed herein, and its unclean hands in and about the subject matter of its claims for royalties, and other misconduct as alleged below, preclude Columbia from recovery of the royalties it claims or from terminating the license agreement. On the contrary, Amgen and Immunex have overpaid royalties to Columbia by mistake, and seek to recover back such royalties.

8. In response to an action filed by Amgen and Immunex against Columbia to determine the invalidity and unenforceability of the '275 patent, Columbia attempted to avoid and delay the determination of these issues. Toward that end, Columbia filed an application in the PTO seeking reissue of the patent, and based on that application, sought a stay of the

litigation (which was denied). When confronted with deadlines for exchange of expert evidence that would evidence the invalidity of the '275 patent because of double-patenting (evidence that Columbia would then be obliged to disclose to the PTO in the reissue proceeding), and approximately two weeks following the Court's Order of August 17, 2004 in this action allowing certain depositions of percipient witnesses whose testimony was to be completed by September 30, 2004 and whose testimony would further evidence Columbia's inequitable conduct, Columbia filed on September 2, 2004, an "emergency motion" to dismiss the challenges to the '275 patent based on a covenant not to sue (the "Covenant") which Columbia contended to mean that there was no longer a case or controversy regarding the challenges to the '275 patent. Columbia's original Covenant was so transparently defective that Columbia has extended it in several ways. However, Columbia has failed and refused to extend the Covenant to include the claims of the '275 patent if they emerge as part of a different patent (for which Columbia has a patent application pending, no. 08/477,159) or to Plaintiffs.

JURISDICTION

9. This action arises under the laws of the United States, and jurisdiction therefore exists under 28 U.S.C. §§ 1331, 1338(a) and 2201, and the Court's supplemental jurisdiction under 28 U.S.C. § 1367(a), because, among other things, Plaintiffs seek a declaration pursuant to the United States Patent Laws, 35 U.S.C. § 271, that a United States patent held by Columbia is invalid and unenforceable, and that Plaintiffs are not infringing any valid and enforceable claim of the '275 patent. Additionally, because the matter in controversy herein between each Plaintiff and Columbia exceeds the sum or value of $75,000, exclusive of interest and costs, and the action is between citizens of different states, jurisdiction exists under 28 U.S.C. § 1332(a)(1).

VENUE

10. Venue is proper in this district under 28 U.S.C. § 1391(b) because a substantial part of the events giving rise to the claim occurred in this judicial district.

THE PARTIES

11. Plaintiff Amgen Mfg., an affiliate of Amgen, is a company having its principal place of business in Juncos, Puerto Rico. It is not a citizen of New York. Amgen Mfg. manufactures EPOGEN® (Epoetin alfa) in the United States and sells that product to Amgen USA.

12. Plaintiff Amgen USA, an affiliate of Amgen, is a corporation having its principal place of business in Thousand, Oaks, California. It is not a citizen of New York. Amgen USA sells EPOGEN and Enbrel® (etanercept) into the United States.

13. Plaintiff Immunex R.I., an affiliate of Amgen, is a corporation having its principal place of business in West Greenwich, Rhode Island. It is not a citizen of New York. Immunex R.I. manufactures etanercept in the United States on behalf of Immunex, a wholly owned subsidiary of Amgen.

14. Defendant Columbia is a New York corporation with its principal place of business in New York, New York.

Facts Common to All Claims for Relief

A. Columbia Obtained U.S. Patents that Expired on August 16, 2000

15. On February 25, 1980, Columbia filed U.S. Patent Application Ser. No. 06/124,513, based upon work performed under grants from the National Institutes of Health, Department of Health and Human Services. That application has resulted in the issuance of several U.S. patents that were assigned to Columbia.

16. The first such patent, U.S. Patent No. 4,399,216 (the "'216 patent"), was issued August 16, 1983, and was entitled "Processes for Inserting DNA into Eucaryotic Cells and for Producing Proteinaceous Materials." The '216 patent identifies Richard Axel, Michael H. Wigler and Saul J. Silverstein as inventors. A true copy of the '216 patent is attached hereto as Exhibit A. The '216 patent expired on August 16, 2000.

17. The second such patent, U.S. Patent No. 4,634,665 (the "'665 patent"), was issued January 6, 1987, to Columbia and was based on an identical disclosure. It was entitled "Processes for Inserting DNA into Eucaryotic Cells and for Producing Proteinaceous Materials," and resulted from a so-called "continuation" application from the application that matured into the '216 patent. A true copy of the '665 patent is attached hereto as Exhibit B.

18. On August 12, 1985, the PTO rejected certain claims in the application which matured into the '665 patent based upon double-patenting in light of certain claims in the '216 patent. In response, Columbia disclaimed the term of any resulting patent beyond the expiration date of the earlier patent. As a result, the PTO issued the '665 patent. Pursuant to the terminal disclaimer, the '665 patent expired on August 16, 2000.

19. The third such patent, U.S. Patent No. 5,179,017 (the "'017 patent"), was issued January 12, 1993, to Columbia and was based on an identical disclosure. It was entitled "Processes for Inserting DNA into Eucaryotic Cells and for Producing Proteinaceous Materials," and resulted from a so-called "continuation" of the application that had led to the '665 patent, which in turn claimed priority to the same application that matured as the '216 patent. A true copy of the '017 patent is attached hereto as Exhibit C. On January 8, 1992, the PTO rejected certain proposed claims in the application which matured into the '017 patent, because of the prohibition of double-patenting in light of certain claims in the '216 patent. In order to secure

allowance of the '017 patent in the face of the prohibition of double-patenting, Columbia filed on April 3, 1992, a terminal disclaimer, disclaiming any part of the resulting '017 patent that would extend beyond the term of the '216 patent. Pursuant to the terminal disclaimer, the '017 patent expired on August 16, 2000.

20. Columbia obtained corresponding foreign patents including European Patent No. 045,809, granted on August 19, 1987, and the national patents based on the European patent. The European patents and other corresponding foreign patents expired on February 25, 2000--twenty years from their priority filing date, which was the filing date of the '216 patent. Columbia also secured corresponding Canadian Patent No. 1179953, which expired on December 27, 2001.

21. From August 16, 1983, when the '216 patent issued, through the expiration of the prior issued Axel patents on August 16, 2000, Columbia profited greatly from these patents. Plaintiffs are informed and believe that Columbia has received hundreds of millions of dollars of royalties by reason of the prior issued Axel patents.

B. The License Agreements with Columbia

22. Effective as of June 1, 1989, Amgen and Columbia entered into a written agreement entitled "License Agreement relating to U.S. Patent No. 4,399,216 *et al.*" Effective as of October 1, 1991, Immunex and Columbia entered into a similar written agreement bearing the same title. The agreements contain nearly identical terms and are hereinafter jointly referred to as the "License Agreement." True copies of these agreements, with amendments, are attached hereto as Exhibits D and E.

23. Among other things, the License Agreement calls for payment of royalties on certain sales of "Licensed Products" as defined by the License Agreement.

24. Additionally, the License Agreement incorporates by reference the same obligations imposed by the United States Government on Columbia pursuant to 35 U.S.C. §§ 200-211, regulations thereunder, and the determination letter to Columbia from the Department of Health and Human Services dated February 24, 1981, a copy of which is attached to the License Agreement as Appendix A. Among those obligations is an obligation imposed on Columbia by the determination letter and 45 C.F.R. § 8.2(b) to refrain from "unreasonable royalties and repressive practices," an obligation imposed on Columbia to avoid any unusual restrictions (45 C.F.R. § 8.0(c)) and an obligation imposed on Columbia to refrain from "unreasonable restrictions or excessive royalties" (45 C.F.R. § 8.1(b)) (collectively referred to below as the obligations to refrain from "unreasonable royalties and repressive practices").

C. Columbia Unsuccessfully Attempted to Extend the Term of its Patents

25. Columbia, not content with its about-to-expire patent monopoly, embarked upon a plan to extend the term of its exclusive rights by a variety of means. In furtherance of this plan, on information and belief, Columbia attempted to bury, in section 2801, chapter 8 of an Agricultural Appropriations Bill, a provision that would have granted Columbia the much-desired extension of the above-referenced Columbia patents.

26. Columbia's efforts to slip the patent extension provision past the public camouflaged in an unrelated appropriations bill, on information and belief resulted in widespread public outcry. As a result of such protests, section 2801 was eliminated from the Appropriations Act as enacted, Pub. L. 106-387, 106th Congress (2000).

27. Plaintiffs are informed and believe, and on such information and belief allege, that Columbia also attempted to include a similar provision in the Department of Defense Appropriations Act, as reported at 146 Cong. Rec. S5033-01 at S5050 (2000). But again this

effort to extend its monopoly failed and no such provision was included in the final Department of Defense Appropriations Act of 2001, Pub. L. 106-259, 106th Congress (2000).

28. When Columbia's lobbying for a patent term extension failed, the prior issued Axel patents expired on August 16, 2000, and their subject matter entered the public domain.

D. After Expiration of the Three U.S. Patents, Columbia Obtained the '275 Patent

29. In parallel with its efforts to prolong its exclusive rights legislatively, Columbia repackaged its earlier patent claims in several iterations of different words in an effort to obtain another patent with claims of the same scope with an additional 17-year term. Columbia could have presented all of these claims in the prior issued Axel patents that have now expired. By not doing so, Columbia attempted to impermissibly extend the protection afforded by its earlier patent claims.

30. In particular, after issuance of the '017 patent on January 12, 1993, Columbia submitted a chain of four consecutive applications eventually leading to issuance of Columbia's fourth patent relevant to this action, U.S. Patent No. 6,455,275 (the "'275 patent") on September 24, 2002. During the prosecution of this chain of applications, responsibility within the PTO for examination of the applications changed six times. Over this nearly ten-year period, Columbia, on eleven separate occasions, proposed claims that the PTO examiner rejected for double-patenting.

31. The '275 patent was issued September 24, 2002, to Columbia, and was based on a disclosure identical to the '216 patent. It was entitled "DNA Construct for Producing Proteinaceous Materials in Eucaryotic Cells" and claims the same priority date as the prior issued Axel patents based on the same parent application. Unlike the '665 and '017 patents, in securing

the '275 patent Columbia did not enter a terminal disclaimer. A true copy of the '275 patent is attached hereto as Exhibit F.

E. Columbia Made Misrepresentations or Misleading Omissions which were Material to the Examination and/or Patentability of the Prior Issued Axel Patents and the '275 Patent

(i) Columbia failed to disclose publications and work known to named-inventors

32. In connection with the prosecution of the prior issued Axel patents and the '275 patent (collectively, the "Axel patents"), on February 23, 1980, Richard Axel, Michael H. Wigler, and Saul J. Silverstein (Axel *et al.*) signed declarations stating that "we verily believe we are the original, first and joint inventors of the invention described and claimed therein; that we do not know and do not believe that this invention was ever known or used in the United States before our invention thereof, or patented or described in any printed publication in any country before our invention thereof." Declarations signed by Axel *et al.* were submitted in connection with the prosecution of each of the Axel patents. When Axel *et al.* signed the declarations, Richard Axel and Saul J. Silverstein were employees of Columbia; Michael H. Wigler had recently left the employ of Columbia.

33. On information and belief, at the time that Axel *et al.* signed the declarations stating that they were the "original, first and joint inventors of the invention described" they were aware that others had used or known, in the United States, methods to transform CHO cells and mouse cells using purified DNA containing genes including amplifiable genes, such as a mutant dihydrofolate reductase ("*dhfr*") gene. On information and belief, at the time that Axel *et al.* signed the declarations they were aware that others had known or used, in the United States, methods to transform eukaryotic cells with dominant selectable markers. On information and belief, at the time that Axel *et al.* signed the declarations, they were also aware that others had

used or known, in the United States, methods to cotransform CHO cells using purified DNA containing genes such as the gene conferring the ability to grow in the absence of proline ("the *pro*+ gene") and the amplifiable ouabain resistance gene.

34. Prior to July 2, 1978, while Dr. P. R. Srinivasan was working in the laboratory of Dr. Louis Siminovitch while on sabbatical from the Department of Biochemistry at Columbia University, Richard Axel, his colleague from the department, phoned him. Dr. Srinivasan wrote a July 2, 1978 letter ("the Lewis & Srinivasan Letter") informing Richard Axel that "Bill Lewis and I have been hard at work on chromosomes and DNA transfer in CHO cells." Dr. Srinivasan further informed Richard Axel that "[t]he markers we have chosen for our study so far are the genes for thymidine kinase, methotrexate resistance and α-amanitin resistance." The Lewis & Srinivasan Letter also referred to Dr. Srinivasan's work with, *inter alia*, DNA from methotrexate resistant mutants of CHO, and notified Richard Axel that "[i]n view of these interests your early experiments will be similar if not identical to our program." The mutant CHO cells contained a mutant *dhfr* gene encoding a methotrexate resistance phenotype, and the *dhfr* gene was known to be an amplifiable gene. Dr. Srinivasan successfully transformed CHO cells with genes including the mutant *dhfr* gene while working in Dr. Siminovitch's laboratory. In September of 1978, Dr. Srinivasan rejoined Richard Axel in the Department of Biochemistry at Columbia University, and thereafter, on information and belief, had occasions to discuss, *inter alia,* departmental activities.

35. The results of Dr. Srinivasan's and Dr. Lewis's CHO cell transformation experiments using a mutant *dhfr* gene encoding a dominant selectable phenotype were presented in Philadelphia, Pennsylvania at the May 1979 Wistar Symposium on "Introduction of Macromolecules Into Viable Mammalian Cells" (the "Lewis & Srinivasan Presentation"). The

proceedings from the May 1979 Wistar Symposium in Philadelphia, Pennsylvania were published in the Wistar Symposium Series, "Introduction of Macromolecules Into Viable Mammalian Cells," Vol. 1 (Alan R. Liss, Inc. 1980). That publication reported the Lewis & Srinivasan Presentation entitled "Transfer of the Dihydrofolate Reductase Gene into Mammalian Cells Using Metaphase Chromosomes or Purified DNA" ("the Lewis & Srinivasan Reference"). On information and belief Michael Wigler and Angel Pellicer, a post-doctoral fellow in the laboratory of Richard Axel, attended the Wistar Symposium in May 1979 and heard details of successful CHO cell transformation experiments involving, *inter alia*, a mutant *dhfr* gene encoding a dominant selectable phenotype, in the Lewis & Srinivasan Presentation.

36. Previously, on or about January 27, 1978, Dr. Sol Goodgal, a professor at the University of Pennsylvania, told Richard Axel, *inter alia*, about his research involving transformation of mammalian cells, including CHO cells.

37. By at least September 1979, Dr. Goodgal had transformed CHO cells with DNA containing a ouabain resistance gene encoding a dominant selectable phenotype ("the Goodgal CHO Transformation Work"). As of at least October 26, 1979, Dr. Goodgal began work on CHO cell cotransformation using the ouabain resistance and *pro+* genes ("the Goodgal Cotransformation Work"). On or about October 26, 1979, Dr. Sol Goodgal told Michael Wigler, *inter alia*, about his successes with transformation of CHO cells using purified DNA containing the ouabain resistance gene. On information and belief, prior to February 25, 1980, Dr. Goodgal's collaborator, Edie Postel, told Michael Wigler, *inter alia*, of their work on cotransformation of CHO cells using the ouabain resistance and the *pro+* genes. It was known to those of skill in the art as of February 25, 1980 that the ouabain resistance gene encodes a dominant selectable phenotype and that the ouabain resistance protein is a glycoprotein. The

ouabain resistance gene is also an amplifiable gene. Dr. Goodgal worked at the University of Pennsylvania and did not owe a duty of confidentiality to Columbia.

38. In May 1980, Dr. Goodgal submitted a manuscript describing his earlier work on cotransformation of CHO cells to the journal "Somatic Cell Genetics," of which Saul Silverstein was a member of the editorial board. On information and belief, Saul Silverstein was aware of Dr. Goodgal's work.

39. Despite Axel *et al.*'s knowledge of, *inter alia*, the Goodgal CHO Transformation and Cotransformation Work and the Lewis & Srinivasan Letter, Presentation and Reference, Columbia failed to disclose any of that information to the PTO during prosecution of the prior issued Axel patents and the '275 patent.

40. Misleading omissions and misrepresentations made by Columbia during the prosecution of any of the prior issued Axel patents were material to the patentability and/or examination of the later issued '275 patent. The '275 patent claims priority to the applications leading to the prior issued Axel patents. In addition, as alleged herein, the claims of the '275 patent are not patentably distinct from claims in prior issued Axel patents. Columbia's misleading omissions and misrepresentations during the prosecution of the prior issued Axel patents were therefore also material to the examination and/or patentability of the '275 patent.

41. The Goodgal CHO Transformation Work, which included transformation of CHO cells using the amplifiable ouabain resistance gene encoding a dominant selectable phenotype associated with resistance to the drug, ouabain, was material to the examination and/or patentability of the prior issued Axel patents and the '275 patent. Axel *et al.* never disclosed their knowledge of the Goodgal CHO Transformation Work to the PTO during prosecution of the prior issued Axel patents and the '275 patent:

a. The Goodgal CHO Transformation Work was material to the examination and/or patentability of claims in the '216 patent. For example, claims 54-73 of the '216 patent each incorporate a limitation requiring transforming a eucaryotic cell with "a molecule which is formed by linking one of said foreign DNA I molecules to a DNA II molecule corresponding to an amplifiable gene for a dominant selectable phenotype not expressed by said eucaryotic cell." As another example, claims 18, 46, and 69 specify that the DNA II is a gene associated with drug resistance. The Goodgal CHO Transformation Work included the transformation of CHO cells using an amplifiable ouabain resistance gene encoding resistance to the drug ouabain. For at least the above reasons, Axel *et al.*'s undisclosed information regarding the Goodgal CHO Transformation Work was material to the examination and/or patentability of the claims in the '216 patent.

b. The Goodgal CHO Transformation Work was also material to the patentability and/or examination of claims in the '665 patent. For example, claim 10 of the '665 patent recites a "DNA II which codes for a selectable phenotype not expressed by said eucaryotic cell" which "comprises a gene associated with drug resistance." The Goodgal CHO Transformation Work included the transformation of CHO cells using an amplifiable ouabain resistance gene encoding resistance to the drug ouabain. In addition, during prosecution of the '665 patent, in response to an August 12, 1985 Rejection of claims 153-155 based on Willecke *et al.*, "Cotransfer of two linked human genes into cultured mouse cells," 73(4) Proc. Nat'l Acad. Sci. 1274 (1976) ("Willecke *et al.* 1976") in view of Nunberg *et al.*, "Amplified dihydrofolate reductase genes are localized to a homogeneously staining region of a single chromosome in a methotrexate-resistant Chinese hamster ovary cell line," 75(11) Proc. Nat'l Acad. Sci. 5553 (1978) ("Nunberg *et al.*"), Columbia responded by distinguishing Willecke *et al.* 1976 and

Nunberg *et al.* because "Nunberg *et al.* does not teach or suggest transforming eucaryotic cells with a DNA molecule" and "Willecke *et al.* do not teach or suggest the use of a DNA II which encodes an amplifiable gene for a dominant selectable phenotype as a means of identifying eucaryotic cells which have been amplified to contain multiple copies of a foreign DNA I." '665 patent prosecution history, 2/11/86 Amendment at 4-5. Columbia could not have distinguished the undisclosed Goodgal CHO Transformation Work on the same basis used to distinguish Willecke *et al.* 1976 and Nunberg *et al.* because, *inter alia*, the Goodgal CHO Transformation Work included the transformation of CHO cells using an amplifiable ouabain resistance gene encoding resistance to the drug ouabain. For at least the reasons above Axel *et al.*'s undisclosed information regarding the Goodgal CHO Transformation Work was material to the examination and/or patentability of claims in the '665 patent.

c. The Goodgal CHO Transformation Work was also material to the examination and/or patentability of claims in the '017 patent. For example, each of issued claims 1-5 of the '017 patent incorporates the limitations "[a] transformed Chinese Hamster Ovary cell which comprises amplified foreign DNA I . . . and amplified DNA II encoding a dominant selectable phenotype not expressed by the transformed cell prior to transformation." The Goodgal CHO Transformation Work included the transformation of CHO cells using an amplifiable ouabain resistance gene encoding resistance to the drug ouabain. For at least the reasons above, Axel *et al.*'s undisclosed information regarding the Goodgal CHO Transformation Work was material to the examination and/or patentability of the claims in the '017 patent.

d. The Goodgal CHO Transformation Work was also material to the examination and/or patentability of claims in the '275 patent. For example, each of the claims of

the '275 patent incorporate the limitations "transformed Chinese Hamster Ovary" cell (issued claims 1-19) or "[a] DNA construct for expression in Chinese Hamster Ovary (CHO) cells" (issued claim 20). As another example, transformed CHO cell claims 4 and 15 of the '275 patent recite a "DNA I" encoding "a proteinaceous material . . . wherein the proteinaceous material is a glycoprotein," while additional transformed CHO claims 16-19 of the '275 patent incorporate the limitation "DNA I corresponding to a gene encoding a glycoprotein of interest" and claim 19 additionally recites that the transformed CHO cell "further compris[es] the glycoprotein of interest." The Goodgal CHO Transformation Work involved transformation of CHO cells with the ouabain resistance gene, and the protein conferring resistance to the drug ouabain was known to those of skill in the art prior to February 25, 1980 to be a glycoprotein. In addition, during prosecution of the '275 patent in response to a double-patenting rejection, Columbia distinguished rejected claims 128-131 on the basis that the claims recited a "species" not obvious from claim 73 of the '216 patent, which was directed generically to a mammalian cell:

> It appears that even if the analysis in the January 31, 2000 Office Action is correct, only claims 126 and 127 would be subject to the rejection. Specifically, claim 73 of the '216 patent recites, generically, a mammalian cell into which foreign DNA I linked to DNA II has been introduced. Claims 128-131 of the subject application recite species which are not obvious from claim 73 of the '216 patent. Accordingly, claims 128-131 should not have been included in the obviousness-type double patenting rejection over claim 73 of the '216 patent.

'275 patent prosecution history, 7/31/00 Amendment at 5 (emphases in original). The species recited in claims 128 and 131 included a construct "for expression in Chinese Hamster Ovary cells," while claim 126 generically recited a construct "for expression in eucaryotic cells" and claim 127 recited a construct "for expression in mammalian cells." Claim 131 issued as claim 20 of the '275 patent, reciting a "DNA construct for expression in Chinese Hamster Ovary (CHO)

cells." The Goodgal CHO Transformation Work included the transfer of purified DNA containing the ouabain resistance gene and the expression of the ouabain resistance gene in a transformed CHO cell. For at least the reasons above, Axel *et al.*'s undisclosed information regarding the Goodgal CHO Transformation Work was material to the examination and/or patentability of the claims in the '275 patent.

42. The Goodgal Cotransformation Work, which included cotransformation of ouabain sensitive CHO cells incapable of growing in the absence of proline using the ouabain resistance gene and unlinked *pro+* gene, was material to the examination and/or patentability of the prior issued Axel patents and the '275 patent. The Goodgal Cotransformation Work was material to the examination and/or patentability of the prior issued Axel patents and the '275 patent for, *inter alia*, the reasons described in ¶ 41 and the following additional reasons:

a. The Goodgal Cotransformation Work was also material to the examination and/or patentability of claims in the '216 patent. As an example, each of claims 31-48, and 51-53 incorporates the limitation "cotransforming said eucaryotic cell with said multiplicity of foreign DNA I and a multiplicity of unlinked foreign DNA II." As another example, during prosecution of the '216 patent, Columbia distinguished references cited by the examiner in a July 14, 1981 Office Action on the basis that those references disclosed "linked" transformation. In response to the examiner's rejection of claims 45-64 (including issued claims 31-48) and 71-78 (including issued claims 51-53) as obvious under 35 U.S.C. § 103 based on Kretschmer *et al.* and Mantei *et al.*, Columbia responded:

> In addition, the argument there advanced in opposition to an obviousness rejection based upon combining the teachings of Kretschmer, *et al.* with those of Wigler, *et al.* (reference S) are also applicable to this rejection, particularly since the Mantei, *et al.* article involves linked DNA which is distinguishable from Applicants' unlinked DNA.

'216 patent prosecution history, 11/5/1981 Amendment at 10. The Goodgal Cotransformation Work included cotransformation of mammalian CHO cells with a DNA I (*pro+*) and unlinked DNA II (ouabain resistance gene). Columbia could not have distinguished the Goodgal Cotransformation Work on the same basis used to distinguish Kretschmer *et al.* and Mantei *et al.* In addition, Columbia responded similarly to the rejection of claims 25-29, 65-68, 70, 101 and 102 (including issued claims 20, 21, 30, 49 and 50) as obvious and/or anticipated under § 102 and § 103 based on Mantei *et al.*, which the examiner asserted showed "eucaryotic cells transformed by linked protein DNA and *TK* DNA. No difference in the transformed cell is seen whether linked or unlinked DNA is used." '216 patent prosecution history, 7/14/81 Office Action at 11:

> With respect to the Mantei, *et al.* reference, Applicants reiterate their position that use of linked DNA is patentably distinguishable from their claimed invention.

Id., 11/5/81 Amendment at 11. Again, Columbia could not have distinguished the Goodgal Cotransformation Work on the same basis used to distinguish Mantei *et al.* For at least the reasons above, Axel *et al.*'s undisclosed information regarding the Goodgal Cotransformation Work was material to the examination and/or patentability of the claims in the '216 patent.

b. The Goodgal Cotransformation Work was also material to the examination and/or patentability of claims in the '665 patent. As an example, each of the claims of the '665 patent recite "cotransforming said eucaryotic cell with said foreign DNA I and with unlinked foreign DNA II" (issued claims 1-15) or "cotransforming a suitable eucaryotic cell with foreign DNA I . . . and with unlinked foreign DNA II" (issued claims 16-23). As another example, issued claim 10 recites that DNA II "comprises a gene associated with drug resistance." The gene for ouabain resistance used by Dr. Goodgal in his work on cotransformation of CHO

confers resistance to the drug, ouabain, while the second gene used by Dr. Goodgal in his cotransformation experiments, the *pro+* gene, was not expressed by the recipient cells prior to transformation, and is not linked to the ouabain resistance gene. In addition, during prosecution of the '665 patent, in response to an August 12, 1985 Rejection of claims 153-155 based on Willecke *et al.* 1976 in view of Nunberg *et al.*, Columbia responded by distinguishing Willecke *et al.* 1976 and Nunberg *et al.* for the following reasons, *inter alia*:

> Willecke et al. do not teach or suggest transforming eucaryotic cells with a DNA molecule that is formed by linking a foreign DNAI molecule, containing a gene encoding a protein, to a DNAII molecule which corresponds to an amplifiable gene for a dominant selectable phenotype which is not expressed by the eucaryotic cell, as in applicants' claim 153. . . . Willecke et al. do not teach or suggest the use of a DNAII which encodes an amplifiable gene for a dominant selectable phenotype as a means of identifying eucaryotic cells which have been amplified to contain multiple copies of a foreign DNAI.
>
> Nunberg et al. teach the amplification of the dihydrofolate reductase (DHFR) gene in hamster ovary cells selected for high resistance to methotrexate by progressively increasing the methotrexate concentration in the culture medium. Nunberg et al. do not teach or suggest transforming eucaryotic cells with a DNA molecule. . . . The hamster ovary cells of Nunberg et al. are not transformed to contain the DHFR gene but rather these cells naturally contain the DHFR gene. Also, the DHFR gene is expressed by the hamster ovary cells before amplification.

'665 patent prosecution history, 2/11/86 Amendment at 4-5. Columbia could not have distinguished the Goodgal Cotransformation Work on the same bases that it distinguished Willecke *et al.* 1976 and Nunberg *et al.*, because the Goodgal Cotransformation Work included the cotransformation of ouabain sensitive CHO cells using the *pro+* gene and an amplifiable ouabain resistance gene encoding resistance to the drug ouabain. For at least the reasons above, Axel *et al.*'s undisclosed information regarding the Goodgal Cotransformation Work was material to the examination and/or patentability of claims in the '665 patent.

c. The Goodgal Cotransformation Work was also material to the examination and/or patentability of claims in the '017 patent. As an example, each of issued claims 1-5 of the '017 patent incorporates the limitations "[a] transformed Chinese Hamster Ovary cell which comprises amplified foreign DNA I . . . and amplified DNA II encoding a dominant selectable phenotype not expressed by the transformed cell prior to transformation." As another example, Willecke *et al.* 1976 and Nunberg *et al.* were cited by the examiner as the basis for rejection under 35 U.S.C. § 103 during prosecution of claims 126-128 in the '273 application leading to issuance of the '017 patent. The Goodgal Cotransformation Work included cotransformation of ouabain sensitive CHO cells using the amplifiable ouabain resistance gene and the unlinked *pro+* gene. For at least the reasons above, the undisclosed information regarding the Goodgal Cotransformation Work was material to the examination and/or patentability of the claims in the '017 patent.

d. The Goodgal Cotransformation Work was also material to the examination and/or patentability of claims in the '275 patent. As an example, each of the claims of the '275 patent incorporate the limitations "transformed Chinese Hamster Ovary" cell (issued claims 1-19) or "[a] DNA construct for expression in Chinese Hamster Ovary (CHO) cells" (issued claim 20). As another example, transformed CHO cell claims 4 and 15 of the '275 patent recite a "DNA I" encoding "a proteinaceous material . . . wherein the proteinaceous material is a glycoprotein," while additional transformed CHO claims 16-19 of the '275 patent incorporate the limitation "DNA I corresponding to a gene encoding a glycoprotein of interest" and claim 19 further recites that the transformed CHO cell "further compris[es] the glycoprotein of interest." The Goodgal Cotransformation Work involved cotransformation of CHO cells with the *pro+* gene and the ouabain resistance gene, and the protein conferring resistance to the drug ouabain